CBER's Bioresearch Monitoring Program

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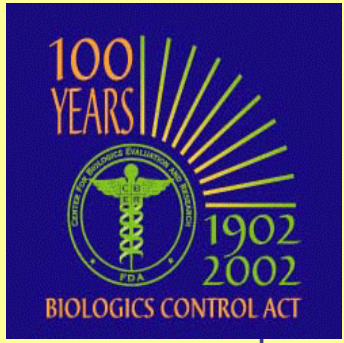
CBER FDA DHHS

CBER 101 Conference

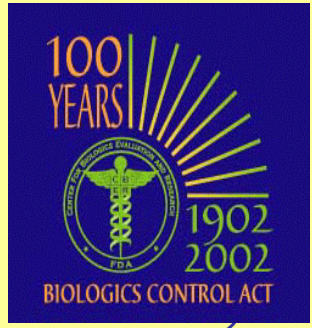
CBER/FDA RAPS DIA

March 26 2003 Rockville, MD



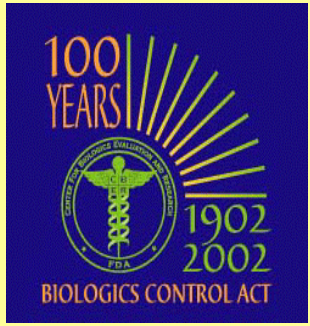
FDA Bioresearch Monitoring (BIMO) Program

- BIMO staff at each FDA Center
- Program coordinated by the FDA Commissioner's Good Clinical Practice Program as well as Office of Regulatory Affairs (ORA)
- Inspections conducted by ORA field staff (along with Center staff, if requested)



FDA's MISSION

Our mission is to promote and protect the public health by helping safe and effective products reach market in a timely manner, and monitoring products for continued safety after they are in use. Our work is a blending of law and science aimed at protecting consumers.



CBER VISION

demonstrating international leadership in science-based regulation through a managed regulatory process, coordinated research and use of partnerships

CBER's BIMO focus

- **Promoting** development and availability of safe and efficient clinical and non-clinical environments;
- **Protecting** human subjects; and
- **Rendering** accurate and reliable data

KEY PRINCIPLES

Our Compliance Goals are achieved through a combination of:

- **Surveillance**
- **Enforcement**
- **Education**

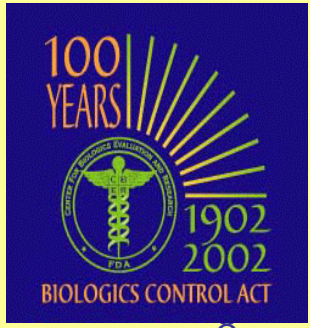
CBER's program --

We request inspections for:

- Non-clinical laboratories
- Clinical investigators
- Institutional review boards (IRBs)
- Sponsors
- Contract research organizations (CROs)
- Clinical trial monitors

BIMO Inspection Assignments

- Submission of BLA
- Referrals from CBER staff
- Referral from another FDA Center
- Complaints from sponsors, IRBs, consumers
- Routine Surveillance based on CBER RISK assessments



Preparing for Inspections from FDA side

- Review Applicable Regulations
- Review Compliance Program
- Review Prior Inspection Record
- Develop Assignment Package

Preparing for Inspections from the "other side"

- What FDA regulations apply?
- What Compliance Program(s) apply?
- What is our Prior Inspection Record?
- Remember: Your FDA inspection is based on our submitted application(s).

FDA Good Clinical Practice Regulations

- Electronic Records; Electronic Signatures (21 CFR Part 11)
- Human Subjects Protection [Informed Consent] (21 CFR Part 50)
- Financial Disclosure by Clinical Investigators (21 CFR Part 54)
- Institutional Review Boards (21 CFR Part 56)
- Investigational New Drug Application (21 CFR Part 312)

FDA Good Clinical Practice Regulations

- Applications for FDA Approval to Market a New Drug (21 CFR Part 314)
- Biological Licensing (21 CFR Part 601)
- Investigational Device Exemptions (21 CFR Part 812)
- Premarket Approval of Medical Devices (21 CFR Part 814)

How does FDA inspect for Regulatory Compliance?

- The Compliance Program Guidance Manuals (CPGM) directs our field personnel in conducting inspectional and investigational activities

- Purpose of each program is to ensure protection of research subjects and integrity of data submitted to FDA in support of a marketing application

How does FDA inspect for Regulatory Compliance?

- CPGM for Clinical Investigators
- CPGM for Sponsors, Monitors, and Contract Research Organizations
- CPGM for Good Laboratory Practice (Non-Clinical Laboratories)
- CPGM for Institutional Review Boards

Preparing for Inspections from the "other side"

- What FDA regulations apply? OK
- What Compliance Program(s) apply? OK
- What about our (and others) prior audits by internal auditors or past inspections by FDA?

What goes WRONG most often at Clinical Sites?

- Most commonly observed deficiencies
  - Failure to follow protocol
    - Violation of inclusion/exclusion criteria
    - Failure to perform required tests
  - Failure to maintain adequate and accurate records
    - absence of supporting source documents
    - inaccurate or incomplete source documents

INSPECTIONAL OBSERVATIONS during ROUTINE INSPECTIONS at Clinical Sites

- Protocol non-adherence
- Failure to report concomitant therapy
- Inadequate and inaccurate records
- Failure to report adverse events
- Inadequate drug accountability
- IRB problems
- Informed consent

After FDA Inspections

- FDA investigators prepare an Establishment Inspection Report (EIR)
- BIMO staff
  - Review and classify EIR
  - Issue correspondence

For FY 2002
CBER Bioresearch Monitoring Branch issued 162 inspection assignments

Institutional Review Boards	7
Clinical Investigators	109
Sponsor Monitor	17
Sponsor / Investigator	22
Good Laboratory Practice	4
Good Manufacturing Practice	3

SUMMARIES of WARNING LETTERS and ENFORCEMENT ACTIVITIES

- In FY 2002, **15 Warning Letters** were issued (as compared to 11 in FY 2001)
- Currently, we are continuing on **disqualification** of clinical investigators

WHAT CRITERIA would trigger FOR-CAUSE INSPECTION?

Suspicion of

- **Fraud** (21 CFR Parts 80; 900; 1000; 1300; 1400)

  or

- **Misconduct** (21 CFR Parts 5; 10; 16; 17; 19; 20; 514; 812; 900)

WHAT SHOULD WE EXPECT - REMEDIAL ACTIONS to INSPECTIONAL OBSERVATIONS?

- Untitled letters
- Titled letters
  - Warning Letters
  - Notice of Initiation of Disqualification Proceedings and the Opportunity to Explain (NIDPOE) Letters

WHAT ELSE COULD result from problems with FDA INSPECTIONS?

- Data unreliable
- Refusal to file (for BLAs)
- Clinical hold
- Termination of IND
- Disqualification
- Application Integrity Policy

CONCLUSION - SINGLE THOUGHT or a "BIG IDEA"

What can you do to improve?

Tips for Successful Programs

Tips for Successful Programs

- **It's all about the Investigational Plan and the Protocol**
- **Understand Elements of Data Quality and Record Quality**
- **Understand Regulatory Responsibilities**
- **Communicate**

Tips for Successful Study:
Investigational Plan and Protocol

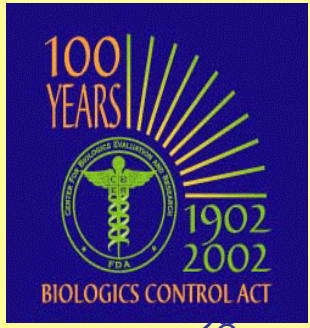
- **Protocol design should be as simple as possible, promoting collection of quality data without compromising study objectives**
  - **Focus on essential data points**
    - **Explain significance in terms of study objectives (efficacy/safety) or subject protection**
  - **Avoid ambiguity and vagueness**
    - **Inclusion/exclusion criteria**
    - **Adverse experiences**

Tips for Successful Study:
Investigational Plan and Protocol

- **Fully understand of limits and importance of strict compliance with protocol requirements**
  - **How much latitude is available for clinical treatment (i.e. Concomitant therapy)?**
  - **Is it ok to use the hospital or clinic protocol for performing routine procedures (i.e., Chemotherapy)?**
  - **Is it ok to skip procedures that are not medically necessary (lab tests, PEs, biopsies)?**
  - **Which protocol procedures can be performed by non-physician study support staff?**

Tips for Successful Study:
Record Quality

- **Minimize the need for transcription**
- **Don’t throw anything away especially originals**
- **Expect the worst**
  - **FDA will be inspecting your records**



Tips for Successful Study:
Record Quality

- **Clearly understand what records are to be maintained and how they should be completed**
  - **Original source data for critical study endpoints**
  - **Use your site's indigenous record-keeping system to the maximum extent possible, discuss this with the sponsor up front**
  - **All records should meet acceptable standards**

Tips for Successful Study:
Data Quality

What are acceptable standards?

- **A** **Attributable**
- **L** **Legible**
- **C** **Contemporaneous**
- **O** **Original**
- **A** **Accurate**

Tips for Successful Study: Understand Regulatory Responsibilities

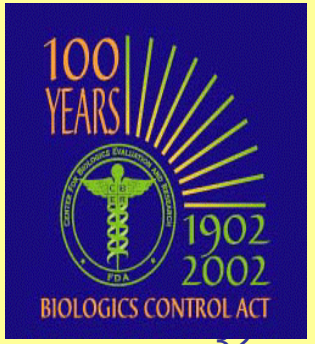
- **Read the following before you sign-on**
  - **ICH GCP Consolidated Guideline**
  - **FDA GCP Regulations**
  - **FDA Information Sheets for IRB's and Clinical Investigators:**

    http://www.fda.gov/oc/oha/irb/toc.html
  - **21 CFR Series**

    http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm

Tips for Successful Study:
Communicate

- **With the IRB**
  - **Protocol changes**
  - **Continuing review**
- **With sponsor and monitors**
  - **Openly address problems**
- **With regulatory authorities**
  - **Understand expectations**
  - **Honor reporting obligations**



CBER 101
EXPECTATIONS

Less history of FDA

and

more hands-on information

EXPECTATIONS

History never looks like history when you are living through it.

John W. Gardner, quoted by Bill Moyers

U.S. Department of Health and Human Services

Food and Drug Administration

Center for Biologics Evaluation & Research

1902 The **BIOLOGICS CONTROL ACT** is passed to ensure purity and safety of serums, vaccines, and similar products used to prevent or treat diseases in humans.

CBER's BIMO Program Staff

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